UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/777,838	02/12/2004	Mark K. Wedel	FMDL0001US	5903

55389 7590 03/24/2010

KNOBBE, MARTENS, OLSON & BEAR, LLP
2040 MAIN STREET
FOURTEENTH FLOOR
IRVINE, CA 92614

EXAMINER	
SHIN, DANA H	

ART UNIT	PAPER NUMBER
1635	

MAIL DATE	DELIVERY MODE
03/24/2010	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/777,838	WEDEL ET AL.	
	Examiner	Art Unit	
	DANA SHIN	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 December 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,7-17,25-42 and 44* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,7-17,25-42 and 44* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Application/Amendment/Claims

This Office action is in response to the communications filed on December 22, 2009.

Currently, claims 1-3, 7-17, 25-42, and 44 are pending and under examination on the merits in the instant case.

The following rejections are either newly applied or are reiterated and are the only rejections and/or objections presently applied to the instant application.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Response to Arguments and Amendments

Withdrawn Rejections

Any rejections not repeated in this Office action are hereby withdrawn.

Maintained Rejections

Claim Rejections - 35 USC § 103

Claims 1-3, 7-17, 25-42, and 44 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Gewritz et al., Patel et al., Sachetto et al., Yacyshyn et al., and Bennett et al. for the reasons of record as set forth in the Office action mailed on June 22, 2009 and for the reasons stated below.

Applicant's arguments filed on December 22, 2009 have been fully considered but they are not persuasive. Applicant argues that the claims are not obvious because the instant rejection is based on misinterpretation of the teachings of the cited prior art references.

Applicant argues that Gewritz et al. do not teach a "reasonable" expectation that alicaforsen can treat CD or UC in an enema formulation by focusing on the negative or uncertain results described in the Gewritz et al. reference. Even if the Gewritz et al. reference were read in bits and pieces by only reading applicant's statements at pages 6-7 of the reply filed on December 22, 2009, there is nothing whatsoever that indicates that there would have been no reasonable expectation such that one would not have expected any therapeutic effect of alicaforsen in an enema formulation. First, the fact that "initial" phase III trials of alicaforsen for CD failed does not suggest that alicaforsen has no therapeutic value because if such were the case, Isis Pharmaceuticals would not have "re-initiated" "new phase III trials" (see the abstract). Further, it is common sense and knowledge in the art that clinical trials often result in unfavorable outcomes or failures due to various reasons including "insufficient dosing" (see page 1401, right column). Again, the fact that "new phase III trials" were "re-initiated" and re-invested after some failures does clearly indicate therapeutic potentials of alicaforsen, not the negativities as alleged by applicant. Second, the "mixed results" pointed out by applicant do not show applicant's alleged lack of a reasonable expectation; rather, the "mixed results" suggest that alicaforsen is more likely to therapeutically effective for treating CD because one was "considerably effective" and the other had no "significant" effect. As such, there would have been a reasonable degree of therapeutic efficacy expected of alicaforsen based on the teachings of Gewritz et al. Third, the fact that the "considerably effective" study used alicaforsen by intravenous infusion, not enema does not indicate that alicaforsen in an enema formulation

would be ineffective in treating CD. It just means that alicaforsen in an enema formulation was not tested in phase II trials. There is nothing that suggests from the "considerably effective" study that alicaforsen in an enema formulation would not have been effective in treating CD. Fourth, the fact that "no results are provided" for the new phase III trials for CD does not imply any negative (or positive) results pertaining to alicaforsen. It merely means that no results were obtained from the newly "re-initiated" phase III trials because the new phase III trials "are reported to be underway." (see page 1401, right column). Fifth, the fact that "no further data are available" for UC treatment does not suggest or synonymous with that the enema formulation of alicaforsen is ineffective for UC treatment. It merely means that nothing was reported from the phase IIa trials performed in France, Belgium and the Netherlands. In no way does it suggest that the enema formulation of alicaforsen cannot treat or is clinically adverse. Sixth, the fact that a suitable concentration of alicaforsen for human CD treatment "has yet to be determined" or that "additional clinical trials are necessary" does not provide any basis for applicant's alleged lack of a reasonable expectation because Gewritz et al. taught that the "overall available data" do suggest some therapeutic benefits of alicaforsen for treating CD and that "safe doses" of alicaforsen can be determined as they were established in the "first double-blind placebo-controlled trial". Lastly, the fact that Gewritz et al. did explicitly suggest that establishing effective enema dosing "would be considerably more desirable" and that alicaforsen remains to be "promising" for treating inflammatory bowel diseases although enema-based alicaforsen was "unproven" does indicate a "reasonable", if not absolute, expectation of success that one could have predicted, at the time the invention was made, some therapeutic effects of alicaforsen in an enema formulation for treating inflammatory bowel diseases. Note that for obviousness under §103, "all that is required is a reasonable expectation of success", and it does not require

"absolute predictability of success". See *In re O 'Farrell*, 853 F.2d 894, 7 USPQ2d 1673 (Fed. Cir. 1988) at 1681. Hence, even reading applicant's selection of negative or uncertain statements disclosed in the Gewirtz et al's reference would not have taught away or discouraged a person of ordinary skill in the art from making and using the enema formulation of alicaforsen for treating inflammatory bowel diseases including UC, CD, and pouchitis.

With regard to applicant's allegation that the examiner has misinterpreted Patel et al., applicant argues that Patel et al. do not teach that pouchitis is a form of IBD but they teach that IBD is distinct from pouchitis by pointing out the abstract and page 1040. Contrary to applicant's argument, and as applicant must be aware as evidenced by the fact that applicant has pointed out the abstract of the Patel et al. reference, the disclosure of Patel et al. relates to "treatment and disease activity in inflammatory bowel disease." (see "Objective" in the abstract), wherein eight of the patients having UC "had a clinical pouchitis" (see "Patients and methods" in the abstract), wherein plasma soluble ICAM-1 levels were "significantly higher" in patients with pouchitis than in those with inactive UC (see "Results" in the abstract). Hence, the fact that the study of Patel et al. relate to treatment of IBD and that they examined and studied patients with pouchitis and that found that ICAM-1 levels were high in patients with pouchitis compared to those with inactive UC is sufficient to indicate that pouchitis is inseparable from and is not distinct from the general terminology of IBD. That is, it is only reasonable that pouchitis is included in the collection of inflammatory bowel diseases. Also, see the last paragraph at page 1037: "The aim of the present study was to determine levels of soluble CAMs in patients with chronic inflammatory bowel disease in relation to its prevalence, disease activity and treatment." As such, the fact that pouchitis patients were examined and studied for soluble CAMs including ICAM-1 indicates that pouchitis is a form of chronic inflammatory bowel disease, absent

evidence to the contrary showing that pouchitis cannot and is not classified as IBD. Further, it is an indisputable fact that chronic pouchitis is an inflammatory gastro-intestinal tract disease that is intimately related to the major form of IBD, ulcerative colitis, as chronic pouchitis was found in patients having UC. In addition, examiner highly doubts that applicant would be able to provide any convincing evidence showing that pouchitis cannot be classified as IBD in view of the teachings of the prior art (see Sachetto et al., US 7,341,741 B1 at column 3, lines 6-10) such that "By IBD we mean Crohn's Disease and ulcerative colitis including ulcerative proctitis, ulcerative proctosigmoi"itis, lymphocytic colitis, intractable distal colitis, ileocolitis, collagenous colitis, microscopic colitis, ***pouchitis***, radiation colitis, and antibiotic-associated colitis." (emphasis added).

With regard to applicant's allegation that the examiner has misinterpreted Sachetto et al., applicant argues that Sachetto et al. do not teach that UC treatment and pouchitis treatment are interchangeable because there are no actual supportive data. As stated hereinabove, pouchitis as well as UC are IBD (see column 3, lines 6-10) and that the invention disclosed in the Sachetto et al. patent relates to "rectally administrable pharmaceutical composition for the treatment or prophylaxis of IBD" comprising "contacting the diseased mucosa of the gastro-intestinal tract" (see column 3, lines 28-43). Furthermore, the mere fact that Sachetto et al. did not disclose actual working examples for UC treatment does not whatsoever indicate that pouchitis treatment and UC treatment are interchangeable. Note that Sachetto et al. disclosed detailed description (see columns 4-5) for making and using pharmaceutical compositions in an enema formulation for treating IBD that includes not only pouchitis but also UC. In addition, Example 4 clearly teaches that the enema formulation was administered to patients who suffered from UC and were thus previously undergone surgery for UC, wherein such patients also "had active chronic pouchitis".

See column 8, line 67. See also Table 1 that specifically lists "Yeasts since diagnosis of Ulcerative colitis". Further, see claims 1-3 that are drawn to an IBD treatment method wherein the IBD is pouchitis (see claim 2) or left sided ulcerative colitis (see claim 3). Hence, examiner does not understand applicant's allegation that the instant rejection is based on the misinterpreted or misstated teachings of Sachetto et al., and it is noted that applicant's such allegation is not supported by persuasive arguments.

With regard to applicant's allegation that the examiner has misinterpreted Yacyshyn et al., applicant argues that the teachings of Yacyshyn et al. do "not support the assertion that an alicaforsen treatment for CD can lead to an alicaforsen treatment for any disease much less pouchitis." First, applicant's attention is directed to the fact that it was never asserted or stated in the last Office action that Yacyshyn et al. suggested using alicaforsen for "any" disease as alleged by applicant. Examiner is unable to find such asserted statement in the last Office action. Applicant is advised to support applicant's such allegation with evidence. Second, Yacyshyn et al. taught that one can determine alicaforsen doses for CD depending on the body weight of a subject being treated. It is true that alicaforsen doses disclosed in the Yacyshyn et al. are relevant to intravenous infusion doses, not for enema formulations. However, the mere fact that Yacyshyn et al. did not disclose enema-alicaforsen doses for CD treatment or for pouchitis treatment does not render the claims any more patentable over non-obvious because the instant rejection is not solely based on the teachings of Yacyshyn et al. but the combination of the prior art references cited in the last Office action as well as the state of the art/technology pertaining to formulating and using alicaforsen for enema administration and treating inflammatory diseases with alicaforsen disclosed by the prior art references. Note that one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references.

See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

With regard to applicant's allegation that the examiner has misinterpreted Bennett et al., applicant argues that Bennett et al. do not disclose therapeutic efficacy of ISIS 2302 in Examples 51 and 53-55, but only in Example 52. Example 51, which describes the overview of phase 2 clinical trials was included in the last Office action for applicant's understanding of the teachings of Bennett et al. with regard to clinical utility potential of ISIS 2302 "in treatment of Crohn's disease in particular, and other inflammatory diseases in general, particularly inflammatory bowel diseases." described in Example 52. If applicant disagrees with including Example 51 as part of the disclosure that teaches clinical use of ISIS 2302, applicant is free to do so. In no way, however, the description of Example 51, wherein "a therapeutic dose in humans" was determined does not negate the fact that ISIS 2302 was clinically tested and shown to be efficacious in reducing ICAM-1 expression in a subject and that the therapeutic dose described in Example 51 was well tolerated in the subject. Applicant argues that there are no therapeutic results in Examples 51 and 53-55. Applicant's attention is directed to the fact that Examples 51-55 were not pointed out in the last Office action just to support the "therapeutic efficacy" of ISIS 2302. See page 8 of the last Office action stating that "ISIS 2302 has been evaluated up to Phase II trials for patients with Crohn's disease and ulcerative colitis". It appears that applicant has taken Examples 51-55 as the disclosure that only supports "therapeutic efficacy" but in fact they were pointed out also to support the clinical evaluations performed for ISIS 2302. Hence, whether or not Examples 51 and 53-55 do not provide clinical data but only describe clinical trials does not show that the examiner misinterpreted and misstated the teachings of Bennett et al. as alleged by applicant. Applicant further asserts that Bennett et al. do not report any therapeutic efficacy of

ISIS 2302 as an enema. Again, it was never asserted or stated in the last Office action that such was taught in the Bennett et al. reference. Further, in response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Applicant contends that the claims are not obvious because Gewirtz et al. stated that further clinical studies are necessary in order to make any "reasonable" assessment of ISIS 2302's clinical value. Again, as noted above, the mere statement that "additional clinical trials are necessary" does not provide any basis for applicant's alleged lack of a reasonable expectation because Gewritz et al. taught that the "overall available data" do suggest some therapeutic benefits of alicaforsen for treating CD and that "safe doses" of alicaforsen can be determined as they were established in the "first double-blind placebo-controlled trial". Lastly, the fact that Gewritz et al. did explicitly suggest that establishing effective enema dosing "would be considerably more desirable" and that alicaforsen remains to be "promising" for treating inflammatory bowel diseases although enema-based alicaforsen was "unproven" does indicate a "reasonable", if not absolute, expectation of success that one could have predicted, at the time the invention was made, some therapeutic effects of alicaforsen in an enema formulation for treating inflammatory bowel diseases. Note that for obviousness under §103, "all that is required is a reasonable expectation of success", and it does not require "absolute predictability of success". See *In re O 'Farrell*, 853 F.2d 894, 7 USPQ2d 1673 (Fed. Cir. 1988) at 1681.

Applicant argues that the combination of the references does not support that the "efficacy of enema formulations of alicaforsen has been established." and merely relies on the

Bennett et al. reference. See page 9. In response, applicant's attention is directed to the fact that applicant has failed to present a clear articulation as to why "any combination of references" fails to support a reasonable expectation that one can make and use a therapeutically effective amount of alicaforsen in an enema formation for pouchitis treatment. Since applicant has not provided proper rebuttal arguments against the entirety of the prior art teachings and the technology/level of knowledge/level of skill disclosed by the prior art teachings, examiner cannot properly address this piece of argument.

Applicant asserts that there is "no reason to assume that all diseases having elevated ICAM-1 can be treated with alicaforsen." Again, examiner does not recognize or notice any statement in the last Office action that states that alicaforsen is an omnipotent drug or a panacea that can treat "all diseases having elevated ICAM-1" as alleged by applicant. All the prior art references used to establish the instant ground of rejection are directly pertinent to or closely linked to inflammatory bowel diseases and potential therapeutic approaches with an antisense compound that reduces the level of ICAM-1 in a subject having an inflammatory bowel disease. Again, every single reference used in the instant rejection addresses one or more aspects of ICAM-1, ISIS 2302, alicaforsen in an enema formulation, methodologies/skills for evaluating pharmacokinentics of ISIS 2302, methodologies/skills for formulating a therapeutically effective dose of ISIS 2302 in an enema with a penetration enhancer, methodologies/skills for diagnosing and evaluating pouchitis based on PDAI scores, IBD, pouchitis, UC, and Crohn's disease. Applicant relies on page 1037 of Patel et al., which states that "Raised levels of soluble forms of these intercellular cell adhesion molecules, namely sICAM-1, sE-selectin and sVCAM-1, have been found in the plasma of a variety of disease states including chronic inflammatory liver disease, diabetes, some carcinomas, allograft rejection and systemic vasculitides." It appears that

applicant attempts to distort the "teachings", "studies", "observations" reported in the Patel et al. reference. Applicant's attention is directed to the fact that the sentence pointed out by applicant is merely a part of "Introduction" section that reviews what was known in the art at the time Patel et al. published their "teachings", "studies", "observations" in 1994. In no way, the entire reference of Patel et al. is insinuating that ICAM-1 reduction is a cure-all for "all" diseases. As explicitly stated in the Patel et al. reference (see the "Objective" for example), the "aim of the present study was to determine levels of soluble CAMs in patients with chronic inflammatory bowel disease in relation to its prevalence, disease activity and treatment." See the next sentence following the applicant's selected sentence at page 1037. Hence, applicant's mere reliance on the comprehensive, art-recognized knowledge in the introductory section to argue that ICAM-1 reduction cannot treat all diseases associated with increased ICAM-1 levels is not pertinent to the "teachings", "studies", "observations" reported in the Patel et al. reference. Furthermore, since the instant rejection is not based on the fact whether ICAM-1 reduction can treat "chronic inflammatory liver disease, diabetes, some carcinomas, allograft rejection and systemic vasculitides" listed in the Patel et al.'s introduction section (at any rate, applicant's attention is directed to the fact that ICAM-1 reduction is indeed shown to be a potential therapeutic approach for many ICAM-1 overexpression-associated diseases as suggested in the Patel et al.'s reference as evidenced by Examples 52-58 of Bennett et al.), applicant's argument alleging that there is no evidence that ICAM-1 reduction can treat all of those diseases is irrelevant to the patentability of the claimed methods pertaining to treating an inflammatory bowel disease, which is pouchitis. Furthermore, applicant continues to isolate one reference at a time and argues that the claims are not obvious. Again, in response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based

on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Applicant asserts that pouchitis is a distinct disease from CD or UC and thus pouchitis treatment is not interchangeable with the treatment of CD or UC by pointing out some passages in the instant specification and Exhibits 2-5. First, applicant has pointed out Example 17 of the specification that teaches that some patients having UC develop pouchitis and then asserts that the fact that UC and pouchitis share some symptoms "does not provide a basis for assuming that treatment successful for one will be successful for the other." Applicant appears to have misunderstood the ground of rejection. Note that even without the teachings of the specification, it was known in the art that some UC patients develop chronic pouchitis. See Patel et al. and Sachetto et al. The instant claims were not found *prima facie* obvious merely because of the clinical link between UC and pouchitis. However, the fact that UC patients sometimes develop chronic pouchitis does provide a reasonable motivation/expectation of success in treating chronic pouchitis by applying a known UC treatment method, only if the UC treatment method resolves the pathological problems associated with chronic pouchitis. As detailed in the last Office action and hereinabove, it was known in the art that reducing ICAM-1 expression is a valid, potential therapeutic approach for treating a chronic inflammatory bowel disease, which includes UC, CD, and pouchitis since all three types of chronic inflammatory bowel diseases are accompanied with increased level of ICAM-1. See Patel et al., Sachetto et al., Gewritz et al., Yacyshyn et al., and Bennett et al. Hence, even if the clinical link between UC and pouchitis development were not known in the art, the fact that reducing ICAM-1 level in a subject is a reasonably efficacious means to treat a chronic inflammatory bowel disease, combined with the fact that ISIS 2302 (an ICAM-1 inhibitor) was shown to have therapeutic values for treating CD and UC provide a

reasonable "basis" such that one can reasonably expect some treatment effects in pouchitis patients having increased ICAM-1 levels by administering a therapeutic dose of ISIS 2302. In addition, it appears that applicant is imposing or begging for an absolute predictability that ISIS 2302 that showed some potential efficacy for CD and UC "will" also work for pouchitis since applicant asserted that the teachings do not "provide a basis for assuming that treatment successful for one ***will*** be successful for the other." (emphasis added). Applicant's attention is directed to the fact that absolute predictability of success is not required for obviousness rejection under 35 U.S.C. 103(a). See *In re O 'Farrell*, 853 F.2d 894, 7 USPQ2d 1673 (Fed. Cir. 1988) at 1681: "all that is required is a reasonable expectation of success", and it does not require "absolute predictability of success". Second, examiner does not understand how Example 17 of the specification that teaches some UC patients develop pouchitis provides support for applicant's asserted nonobviousness of the claims. A careful reading of Example 17 in the specification reveals that pouchitis is indeed associated with over-expressed ICAM-1, which was a known, published fact dating to 1994. See Patel et al and paragraph 0312 of the specification (Example 17). Furthermore, Example 17 (see paragraphs 0312-0313) discloses that ISIS 2302 is used to reduce ICAM-1 expression in a pouchitis patient and that it was known in the art that a therapeutically effective amount of ISIS 2302 in an enema formulation showed some clinical efficacy in animals of "inflammatory bowel disease." and that the pouchitis treatment evaluation was "chosen on the basis of ongoing clinical trials in patients with active ulcerative colitis." As such, the very disclosure of the specification pointed out by applicant in support of applicant's groundless allegation that one cannot use UC treatment method to treat pouchitis or that one cannot treat pouchitis because reduction of ICAM-1 cannot treat a disease merely because the disease is associated with raised ICAM-1 (see page 9 of the reply) in fact teaches that applicant's

allegations are merely applicant's own opinions and do not amount to anything that is scientifically, rationally formulated conclusion. Again, it is coincidentally found, thanks to applicant's specific selection of Example 17 of the specification, that the combination of the prior art references applied in the instant rejection does indeed provide a reasonable basis for one of ordinary skill in the art to use an art-recognized chronic inflammatory bowel disease treatment method (e.g., ISIS 2302-based UC treatment method) to treat pouchitis by reducing the level of ICAM-1, which was known to be over-expressed in pouchitis, UC, and CD. See the detailed 103(a) rejection rationale in the last Office action, which is reiterated hereinabove. As such, applicant's allegations, assertions, and arguments are counterintuitive to what a person of ordinary skill in the art would pursue when seeking pouchitis treatment based on the combination of the prior art cited in the instant rejection and the methodologies, skills, and techniques available in the art at the time the invention was made. Third, none of Exhibits 2-5 shows that reducing ICAM-1 that is found over-expressed in patients with pouchitis as well as those with UC or CD by ISIS 2302 administration in an enema formulation would not lead to pouchitis treatment. That is, no Exhibit shows that ISIS 2302-based UC treatment or ISIS 2302-based CD treatment was known to be inapplicable or unsuitable to treat pouchitis, thereby proving applicant's merely asserted argument that "their treatments are not interchangeable." Furthermore, it was never asserted or stated in the last Office action that pouchitis is the same or identical or indistinguishable or indistinct disease from CD or UC. Rather, it was indicated that pouchitis is an art-recognized chronic inflammatory bowel disease, just like CD or UC is, and that pouchitis is known to be associated with increased level of ICAM-1, just like CD or UC is. Hence, applicant's attempt to show that pouchitis is a distinct disease from CD or UC bears no fruit or does not support applicant's alleged nonobviousness because it was known in the art that

pouchitis in and of itself is ***a*** chronic inflammatory bowel disease independent from CD or UC such that some patients with UC further develop active, chronic pouchitis. See Patel et al. and Sachetto et al. In addition, applicant's attempt to show that the pouchitis treatment is not interchangeable with others does not support applicant's alleged nonobviousness because none of the Exhibits addresses applicant's asserted non-interchangeability of the treatment methods. For example, Exhibit 2 taught that UC can be treated with anti-inflammatory compounds and immune-suppressants, and Exhibit 4 taught that CD can be treated with anti-inflammatory compounds and immune-suppressant, and Exhibit 3 taught that pouchitis is an inflammatory disease of the pouch. Hence, it is questionable why an anti-inflammatory compound-based or immune-suppressant-based CD or UC treatment method would be inapplicable to an inflammatory bowel disease, which is pouchitis. Applicant relies on Exhibit 3 to assert that UC or CD treatment cannot be used to treat pouchitis because Exhibit 3 taught that pouchitis is "primarily treated with antibiotics or probiotics." Applicant is correct that pouchitis treatment method has been primarily limited to antibiotics-based treatment, which had been found unsuccessful or unsatisfactory for those with chronic pouchitis. See column 1 of Sachetto et al., which teaches the following: "Currently, there is no satisfactory treatment for patients with chronic pouchitis who fail to respond to empiric antibiotic therapy." Nevertheless, applicant's mere conclusion that UC or CD treatment method cannot be used for pouchitis because pouchitis is primarily treated with antibiotics/probiotics merely based on Exhibit 3 is found unpersuasive because antibotics/probiotics-based treatment was known to be unsatisfactory for chronic pouchitis as taught by Sachetto et al. Furthermore, there is no evidence of record in applicant's arguments and Exhibits that shows that UC/CD/chronic pouchitis treatment methods are not interchangeable, thus contradicting the teachings/claimed inventions of Sachetto et al. See claims

1-4, 8, 11-12, and 14, wherein claim 1 is broadly drawn to treating an IBD with a pharmaceutical compound, wherein claim 2 specifies the IBD as pouchitis, wherein claim 3 specifies the IBD as left sided ulcerative colitis, wherein claim 4 specifies the IBD as Crohn's disease, wherein claim 8 and 14 specify that the pharmaceutical compound is formulated for rectal administration, wherein claims 11-12 specify that the pharmaceutical compound comprises HPMC for enema formulation (e.g., liquid enema, foam enema). In addition, note that Exhibit 4 taught that IBD therapeutic approaches and options are constantly evolving as there have been "great advances in the understanding of inflammatory bowel disease". See the first page. Hence, applicant's mere reliance on the conventional therapeutic options for CD, UC, and pouchitis, while completely dismissing the instant ground of rejection (the association between ICAM-1 level and pouchitis, CD, and UC, and the state of the art regarding ISIS 2302) does not show applicant's asserted nonobviousness of the instantly claimed methods. Since pouchitis was already known to be a distinct IBD that is separate and independent from CD or UC, and since there is no evidence of record showing that an ICAM-1 inhibitor cannot be used to treat chronic pouchitis as it was shown to be potentially effective for CD or UC treatment, applicant's arguments based on Exhibits 2-5 (i.e., pouchitis is distinct; pouchitis is treated with antibotics whereas CD or UC is treated with anti-inflammatory compound) do not add anything substantial to applicant's preceding arguments. Again, it is noted that applicant has failed to show the asserted nonobviousness in view of the totality of the combined teachings of the prior art references; that is, applicant has completely ignored the fact that although pouchitis is an art-recognized IBD in and of itself independent from CD or UC (see Patel et al. and Sachetto et al.), pouchitis, similar to CD and UC, was known to be an inflammatory disease having elevated levels of ICAM-1, and that reducing mucosal inflammation in the pouch thereby reducing the PDAI score for effective

chronic pouchitis treatment was an art-recognized goal (see Sachetto et al.), and that it was explicitly suggested that non-antibiotics-based treatment method can be interchangeably used to treat pouchitis, left-sided UC, and Crohn's disease wherein a pharmaceutical composition is formulated in an enema formulation and rectally administered (see Sachetto et al.).

Lastly, applicant argues that the claims cannot be obvious because "the claimed methods have unexpected results that are sufficient to demonstrate nonobviousness." and points out the results in Example 17 of the specification, which describes that an enema formulation of ISIS 2302 resulted in remission of 58% of patients. Applicant states that this result is "particularly surprising" because the patients were nonresponsive to other therapies, and thus ISIS 2302 in an enema formulation "provided a successful treatment for a chronic disease that ***currently has no other therapy available***" (emphasis added). First, applicant's attention is directed to the fact that the non-responsive, unsatisfactory, conventional therapeutic strategy for treating pouchitis (e.g., antibiotics-based treatment) has long been recognized in the art and that the inventors of the present application are not the first ones to recognize the need to improve the conventional pouchitis therapy. See Sachetto et al. Second, contrary to applicant's argument that there is "no other therapy available" that has successfully treated pouchitis that was formerly unresponsive to other therapies, there is at least the method of Sachetto et al. who disclosed that their method is "particularly surprising in view of the fact that the patients were refractory to conventional therapy." See column 10. Third, as such, the mere fact that ISIS 2302 was able to reduce PDAI scores for patients who had been unresponsive to other therapies is not "particularly surprising" as alleged by applicant, because there is at least one other pouchitis treatment method in the art that successfully treats patients who had been refractory or unresponsive to conventional pouchitis therapy. Fourth, even if there were no such "particularly surprising" results disclosed in

the Sachetto et al. reference, the mere fact that ISIS 2302 was able to treat some patients does not show the alleged unexpected results because ISIS 2302, which reduces ICAM-1 level, was reasonably expected to have some therapeutic effects given the fact that chronic, active pouchitis patients have increased, over-expressed ICAM-1 levels, further in view of the fact that ISIS 2302 was shown to reduce inflammation for CD and UC patients, and thus would be reasonably expected to reduce mucosal inflammation in the pouch of patients with chronic pouchitis, thereby reducing clinical symptoms and the PDAI score of the patients. Hence, the fact that ISIS 2302 was able to result in some therapeutic effects for chronic pouchitis patients as shown in Example 17 of the instant specification is consistent with what was suggested and taught in the art, not contrary to or conflicting with the teachings of the prior art cited in the instant rejection. Furthermore, as stated above, anti-inflammatory function of ISIS 2302 and reduction of ICAM-1 in patients with chronic pouchitis were reasonably expected. Even if the 50-58% remission rate is viewed as unexpected results as alleged by applicant, such results are not commensurate in scope with the claims because the claims are not drawn to increasing remission rates; the claims are merely drawn to treating pouchitis, wherein the "treating" aspect involves various physiological aspects such as reducing occurrences of clinical symptoms, thereby reducing a PDAI score in a subject. Note that the "objective evidence of nonobviousness must be commensurate in scope with the claims which the evidence is offered to support." See MPEP 716.02. Furthermore, even if the claims were strictly drawn to a method of increasing remission rates in pouchitis patients such that the claims are written to be commensurate in scope with the results in Example 17, the claims would still be found *prima facie* obvious because it was known that ISIS 2302 was capable of increasing remission rates when used to treat inflammatory bowel diseases such as Crohn's disease. See columns 69-70 of Bennett et al., which show that ISIS

2302 reduced a CDAI score for patients having CD and that 47% (7 out of 15) of the ISIS 2302-treated patients were in remission at the end of the 26-day treatment period, wherein 5 of the 7 subjects (thus 33%) remained in remission at day 180. Furthermore, Yacyshyn et al. reported similar remission rates for ISIS 2302-based CD treatment and taught that "Clinical remission rates correlated with the patient's achieved drug exposure, and subjects with high drug exposure had significantly higher remission rates than placebo.", and therefore one can use higher ISIS 2302 doses "for clinical effect and achievement of the desired drug exposure levels." See page 1762, right column. Hence, even if the claims are amended to incorporate applicant's alleged unexpected results regarding remission rates, the claims would be obvious in view of the combined teachings of the prior art references, especially in view of Yacyshyn et al. who taught that one of ordinary skill in the art can optimize the ISIS 2302 dose to achieve clinical remission rates. Again, there is nothing in any of the cited references that suggests that the failure of ISIS 2302 in pouchitis treatment is highly likely or is reasonably expected. Instead, the combination of the references reasonably establishes a reasonable expectation of success in using a therapeutically effective amount of ISIS 2302 compound in an enema formulation for pouchitis treatment for the reasons of record and as detailed hereinabove.

In view of the foregoing, since applicant's arguments are not found persuasive at all, and since applicant has failed to point out or provide a clear articulation as to how the "combination" of the prior art references (the ground of rejection), not individual references, fails to render the claimed methods obvious, this rejection is maintained.

Double Patenting

Claims 1-3, 7-17, 25-42, and 44 remain rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-2 and 4-9 of 11/720,745 for the reasons of record as set forth in the Office action mailed on June 22, 2009 and for the reasons stated below.

Applicant has not provided any rebuttal arguments addressing the supposed errors of this rejection, nor has applicant filed a signed terminal disclaimer. Hence, this rejection is maintained.

Conclusion

No claim is allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to DANA SHIN whose telephone number is (571)272-8008. The examiner can normally be reached on Monday through Friday, 7am-3:30pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Fereydoun Sajjadi (Acting SPE) can be reached on 571-272-3311. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Dana Shin
Examiner
Art Unit 1635

/Dana Shin/
Examiner, Art Unit 1635